arising from the central hydrophobic core, and precipitated by the residues belonging to the N-terminal region. Adaptive biasing force based potential of mean force (PMF) calculations estimating the free energy changes as the peptide strands collapse towards each other demonstrate that the SWCNT causes the 'open' and the 'collapsed' states to be in near equilibrium, by bringing down the energetic cost of 'loop opening'. The observed phenomena of peptide localization and decreased propensity for loop collapse could have important implications for site-directed drug delivery and for altering the kinetics of the peptide's self assembly.

3716-Pos Board B577

Multiscale Simulation of Polyglutamine and the Effect of Neighboring Amino Acids on Oligomerization

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Several proteins possess a segment of amino acids composed of successive glutamines. In many, this segment affects the native folding when expanded above 35 to 40 glutamines. Such effect is associated to neurodegenerative diseases such as Huntington's in which the huntingtin protein misfold. As the huntingtin protein has over 3000 amino acids, it is easier to focus on the glutamine sequence alone as well as part of the neighboring amino acids to this segment. Several experiments characterized the folding of polyglutamine with various amino acid lengths, yielding sometimes contradictory structural and dynamical information. It is safe to say that, at the moment, the early oligomerization is still not clearly understood at an atomic level. To address this question, we present molecular dynamical simulations on various polyglutamine segments from 30 to 40 glutamines with and without neighboring amino acids to assess their importance on folding and fold stability. To reach relevant time-scales, we combine simulations using a coarse-grained model as well an all-atom model with explicit solvent.

3717-Pos Board B578

Monitoring the Mechanism of Fiber Assembly of AB Peptides in Alzheimer's Disease (AD) by Two-Dimensional Ultraviolet (2DUV) Spectroscopy

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Understanding the aggregation mechanism of amyloid fibrils is a critical step in the investigation of several neurodegenerative disorders associated with the misfolding of proteins. In a previous study (Rojas *et al.*, JMB 2010 404, 537–552), the growth mechanism of β-amyloid peptide fibrils which is associated with Alzheimer's disease (AD), was successfully modeled by using a physics-based coarse-grained united-residue model and molecular dynamics (MD) simulations. We report a simulation study of coherent two-dimensional chiral signals based on the trajectories obtained by Rojas *et al*. to monitor this growth mechanism at different simulation times. Far ultraviolet signals (FUV)(λ = 190–250 nm) originated from the backbone $n\pi^*$ and $\pi\pi^*$ transitions, and near ultraviolet signals (NUV) ($\lambda >= 250$ nm) are associated with aromatic side-chains (Phe and Tyr). These signals display distinct cross peak patterns in the two-dimensional spectra that can be used, in combination with MD, to monitor local dynamics and conformational changes in the secondary structure of Aβ peptides during the aggregation process. 2DUV total chiral signals in the aggregation process are combinations of subset of chiral signals from a monomer Aβ peptide, an amyloid fibril and the interactions between them.

3718-Pos Board B579

Conformational Transition Pathways of Adenylate Kinase Explored by the String Method

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Large-scale conformational changes in proteins involve barrier-crossing transitions on the complex free energy surfaces of high-dimensional space. Here we show that, by combining the on-the-fly string method and the multi-state Bennett acceptance ratio (MBAR) method, the free energy profile of a conformational transition pathway in Escherichia coli adenylate kinase can be accurately determined. The minimum free energy paths (MFEPs) of adenylate kinase were searched by the on-the-fly string method in 20-dimensional space spanned by the 20 largest-amplitude principal modes, and the free energy and various kinds of average physical quantities along the MFEPs were successfully evaluated by the MBAR method. The influence of ligand binding on the MFEPs was characterized in terms of rigid-body motions of the LID and AMPbd domains. It was found that the LID domain was able to partially close without the ligand, while the closure of the AMPbd domain required the ligand binding. The transition state ensemble of the ligand bound form was identified as those structures characterized by highly specific binding of the ligand to the AMPbd domain, and was validated by unrestrained MD simulations. It was also found that complete closure of the LID domain required the dehydration of solvents around the P-loop. These findings suggest that the interplay of the two different types of domain motion is an feature in the conformational transition of the enzyme.

3719-Pos Board B580

Conventional and Accelerated Molecular Dynamics Simulations of *Staphylococcus Aureus* Sortase A

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The targeting of surface proteins to the cell wall, necessary for the full virulence of Gram positive bacteria, can be traced back to the actions of sortase enzymes. These enzymes recognize a specific sorting sequence in proteins destined to be displayed on the surface of the bacteria, and catalyze the transpeptidation reaction that results in the attachment of the protein to a cell wall precursor molecule. With the rise of antibiotic resistant strains of bacteria, sortase enzymes are promising new drug targets. Specifically, in light of the growing emergence of methicillin resistant *Staphylococcus aureus* (MRSA), we are looking at *Staphylococcus aureus* Sortase A (SrtA). SrtA cleaves proteins at the LPXTG sorting signal and attaches them to lipid II. Here, we have used both conventional and accelerated molecular dynamics simulations to simulate the enzyme in its apo and holo (bound to the LPATG sorting signal) states. Results reveal the importance of loop motions of which are situated proximal to the active site, specifically the β6/β7 and β7/β8 loops, and suggest dual functionality of the catalytic arginine residue. Additionally, in a subset of the holo simulations we observe movement of the sorting signal away from the active site to distinct metastable states and find that motions of the enzyme in the accelerated molecular dynamics simulations suggest an induced fit binding mechanism. These results improve our understanding of the functioning of SrtA and will ultimately aid in the development of new drugs to combat MRSA infections.

3720-Pos Board B581

Classical Force Field Development and Molecular Dynamics of [Nife] Hydrogenase

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An understanding of the force-field parameters necessary to describe metal clusters in [Ni-Fe]-hydrogenase enzymes currently limits an ability to use classical molecular dynamics (MD) simulations to understand how changes in the coordination geometry around the metal centers promote catalysis. Using density functional theory (DFT), we have developed force-field parameters for three catalytic states of the [Ni-Fe] active site as well as the reduced and oxidized states of the three Fe/S clusters. Calculations were made using small model clusters that approximate the protein environment, respectively replacing cysteinate and histidine coordinating side-chains with thiolates and imidazole. Parameters were tested using 25 ns MD simulations of gas-phase model clusters and classical harmonic frequency analysis. Matching of DFT and MD normal modes verified that the derived force field parameters reproduce the DFT modes and frequencies, even the low-frequency torsion modes that couple with protein backbone motion. The utility of the determined force-field parameters was further established in situ using explicit-solvent, all-atom, 25 ns MD simulations of [Ni-Fe] hydrogenase in three catalytic states (Ni-A, Ni-B, and Ni-C). These results establish the utility of the derived force-field parameters, and provide the basis for testing current models that suggest changes in the coordination geometry of the active site metals promotes catalysis.

3721-Pos Board B582

Nano-Scale Mechanics of Nacre: Forces at Protein-Crystal Linkages and Flaws

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The major constituent of nacre, calcium carbonate (CaCO3) in form of aragonite, is intricately embedded into a soft matrix of protein and chitin, resulting in a highly mechanically robust hierarchical structure. (1) A novel forcefield for aragonite has been developed in this study, which well captures the shear and elastic moduli of the aragonite. Most importantly, the new set of parameters features a calcium ion charge of +1.668, reflecting the partial charge transfer effect in condensed matter. The newly developed CaCO3-water interaction parameters also yield accurate descriptions of water coordination. (2) Our

Molecular Dynamics simulations using this forcefield predict a per-Asp-residue rupture force from aragonite surface of 60 pN, which agrees with experimental results.(3)
Based on our newly developed forcefield parameters, more realistic computational models of nacre were built and used to study the mechanical properties of an aragonite tablet. A state-of-the-art simulation technique, Force Distribution Analysis (FDA) (4), together with a continuum modeling method, Finite Element Analysis (FEA), were employed for the first time to study inorganic models here. The atomic stress concentration around the structural flaws in the mineral tablet in our simulations from the two methods showed good agreements. Combining FDA with FEA, our research will widen the understanding for the mechanically enhanced bio-composite materials on multi-scale level.
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3722-Pos Board B583
MD Simulations Reveal Ultrafast Dielectric Compensation by Water of Large Stokes Shifts from Charged Groups in Staphylococcal Nuclease
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We present intriguing new 40-ns MD simulations with quantum mechanical (ZINDO) treatment of the partially buried tryptophan (Trp) residue in Staphylococcal nuclease. Two lysine residues (K110 and K133) and a glutamate residue (E129) lie close to the Trp, each of which would produce a redshift in the fluorescence wavelength of tens of nm due to strong electrostatic interaction with the large excited state dipole. Remarkably, experiments have shown that individual mutations of these charged residues to alanine have at most a 1 nm effect on the fluorescence emission maximum. Earlier simulations from our group on the wild type (WT) protein showed that much of the large red shift expected from the charged groups was canceled by collective blue shifting interactions from water, so that the wavelength was predicted correctly. The much longer simulations reported here on WT and each of the mutants also predict the same average wavelength within 2 nm. For WT and E129A, the net collective electrostatic interaction from dozens of waters–extending out to 15 Angstroms–contribute a blue shift of ~20 nm, which when added to the ~60 nm red shift contributed by protein, correctly predicts the observed wavelength. For the other mutants, the red shift from protein residues is much smaller, and only a small red shift comes from water. Fast (10 fs), large-amplitude (40 nm) fluctuations of both the protein and water contributions are observed in all cases. The water and protein fluctuations are strongly anti-correlated in every case.

3723-Pos Board B584
Differential Dehydration of Hydrophobic Nanotubes in Aqueous Urea and Guanidinium Chloride Solutions: Implications for Protein Denaturation Mechanism
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This atomistic molecular dynamics simulation study aims to obtain a comparative view of the protein unfolding mechanisms using two chemically different denaturants, urea and guanidinium chloride, by elucidating their interactions with purely hydrophobic carbon nanotubes mimicking protein cores. For this purpose, simulations of carbon nanotubes were carried out in 6M aqueous guanidinium chloride and compared directly with earlier simulations performed in 8M aqueous urea (Das et al., J. Phys. Chem. B 2010, 114, 5427-5430). Preferential denaturant intrusion resulting in dehydration of the nanotube core was found in both denaturant solutions. Further interaction energy analysis reveals that this chemical denaturant-induced nanotube dehydration is primarily driven by the direct dispersion interaction mechanism, during which a denaturant forms stronger dispersion interaction with hydrophobic nanotube than water. We observed more complete and diameter-independent drying of the nanotube interior in urea than in guanidinium chloride. The partial drying of the hydrophobic core can be attributed to guanidinium's better hydration and weaker self-association compared to urea, as well as to its moderate ion-pairing with strongly hydrated chloride ions. The results from the present simulation study propose an initial ''dry globule''-like transient intermediate formation as a general pathway during chemical denaturant induced protein unfolding. However, the molecular details of this kinetic intermediate can be modulated by the microscopic properties of the chemical denaturant used, as well as by the size and chemical nature of the protein.

3724-Pos Board B585
ATP Inhibition of Insulin-Degrading Enzyme: A Computational Study
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Alzheimer's Disease (AD) is a neurodegenerative disease associated to abnormal formation and accumulation of tangles of the amyloid-beta (AB) peptide in specific brain regions connected to memory and cognitive functions.[1]
Insulin Degrading Enzyme (IDE) is a zinc metalloprotease physiologically regulated by ATP, through a still uncertain mechanism. Its ability to degrade insulin and AB has been investigated for the development of drugs for AD, and understanding this mechanism of activation/inhibition of IDE by ATP can open pathways leading to new therapies.[2]
We show blind docking results, obtained using the program AutoLigand in AutoDockTools, which located seven possible sites of ATP binding in the IDE, from which only three seem likely to influence the mechanism of action of this metalloprotease. We also present Molecular Dynamics and QM/MM simulations aimed at understanding this mechanism of IDE inhibition. Finally, we discuss the action of the enzyme towards degrading AB in the presence or absence of ATP.

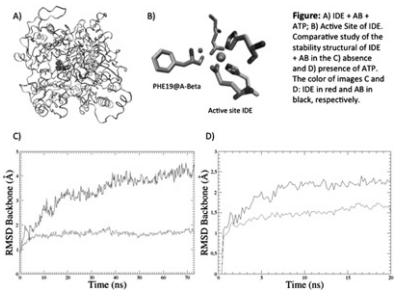

Figure: A) IDE + AB + ATP; B) Active Site of IDE. Comparative study of the stability structural of IDE + AB in the C) absence and D) presence of ATP. The color of images C and D: IDE in red and AB in black, respectively.

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Support: CAPES, FACEPE

3725-Pos Board B586
Molecular Dynamics of the Dengue Virus NS3/NS2b Protease
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Dengue is a vector tropical disease affecting millions of people, and may lead to death. Brazil is the country with the highest number of dengue and dengue hemorrhagic fever (D/DHF) cases combined.[1] In the sixth more populated country in the world, Pakistan, dengue has infected over 12,000 people and killed over 125 in 2011 alone.[2]
Unfortunately, there are no specific medicines for the treatment of D/DHF and, once infected, the WHO recommendations are limited to observation and symptomatic treatment. Recent efforts have revealed a series of proteins essential to the dengue virus's life cycle, which may be used as targets for new medicines.[3]
The aim of the present work is to understand the mechanism of action of such an enzyme, nonstructural protein NS3 protease complexed with the cofactor NS2b (NS3/NS2b), responsible for cleaving the viral polyprotein during the virus replication step, and the identification of molecules capable of effectively inhibiting this enzyme, thus preventing the virus from replicating.We will show molecular dynamics simulations of the NS3/NS2b complex, alone and in the presence of the substrate (Boc-Gly-Arg-Arg-AMC) in the active site, as well as hybrid QM/MM simulations for understanding the enzymatic mechanism.
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Support: CAPES, FACEPE

3726-Pos Board B587
Fatigue at the Molecular Scale
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The influence of force on the stability of inter- and intramolecular bonds has been studied in great detail. Experiments, e.g. with AFMs or the Biomembrane Force Probe, have shown that the relationship between the lifetime of biomolecules and applied forces is well described by the Bell equation. However, rather than experiencing a constant (or continuously increasing) force, some biomolecules are subject to repeated force cycles. For instance, myosin motors in muscles experience millions of force cycles over their lifetime. At the macroscopic level, repeated stress cycles can lead to 'fatigue failure'. Fatigue failure originates in permanent micro-damages and occurs at subcritical stress levels, provided that